PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT-7155	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IT 03/00328	International filing date *(day/month/year)* 28.05.2003	Priority date *(day/month/year)* 31.05.2002
International Patent Classification (IPC) or both national classification and IPC C07D491/22		
Applicant SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.p.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the opinion
   II ☐ Priority
   III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   IV ☒ Lack of unity of invention
   V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   VI ☐ Certain documents cited
   VII ☐ Certain defects in the international application
   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.12.2003	04.10.2004
Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Goss, I Telephone No. +49 89 2399-8292

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT 03/00328

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-25 as originally filed

Claims, Numbers

1-18 as originally filed

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1(partially)

   because:

   ☒ the said international application, or the said claims Nos. 1(partially)3,5,8 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1(partially),2,4,10 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1,2,4,10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1,2,4,10
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV

Lack of unity of invention

The **International Searching Authority** found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1(partially),2,4,10

   Compounds of general formula (I) and intermediate for the production thereof

   1.1. Claims: 1(partially),2,4
   Compounds of general formula (I) being homocamptothecins further modified at the 7 position (R1 cannot mean H)

   1.2. Claim : 10
   7-(dimethoxymethyl)camptothecin claimed as intermediate which, however, does not satisfy the criteria for intermediates to be considered unitary with the end product

2. Claims: 1 (partially), 3,5,8

   Compounds of general formula (II)

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

1. The application in suit refers to several different chemical families of compounds and their use (see the list of inventions defined above) being claimed as active agents endowed with topoisomerase I inhibiting activity useful in the treatment of various related diseases.

2. According to Rule 13(2), 1st sentence, PCT, the requirements of unity of invention in the sense of a technical relationship may be met, when all claimed alternatives belong to a class of compounds which may be expected to behave in the same way in the context of the claimed inventions ("MARKUSH-claims").

The technical relationship involves those common special technical features that define a contribution over the state of the art (Rule 13(2), 2nd sentence, PCT).
However, such contribution cannot be recognized on the basis of this expectation if members of the class have already been shown in the prior art to behave in the manner disclosed in the application and/or if the claimed families of compounds do not display a common technical/structural feature. As described above in the present case some of the claimed families of compounds share the N-heterocycle-containing tetracyclic ring wherein the lactone portion is either a 7-/8-membered lactone ring or a 5-membered ring and R1 may be H or a 7-oxime group. However many 7-membered lactone derivatives unsubstituted at position 7 are already known from the prior art. Moreover, since from many documents cited the homocamptothecin part on one hand is considered the pharmacophoric group and the specific 7-oxime group on the other shows favourable characteristics for a better activity, only these groups combined may be a common technical feature which can be considered the common special technical feature as defined in Rule 30(1)(2) EPC.

3. As far as the first invention as defined above is concerned, the compounds of chemical formula I and those of many citations overlap. The structural difference to the many novelty destroying prior art documents resides mainly in the provision of the compounds defined above under 1.1. The technical problem due to the overlap is thus considered to be the provision of further camptothecin analogs wherein the lactone portion is modified and the 7 position is optionally substituted by and oxime derivative.

However, such contribution cannot be recognized a posteriori on the basis of this expectation if members of the class have:
a) a different core structure (7-/8-membered lactone ring namely well known in the prior art to behave in this specific pharmaceutical field) and b) if the claimed families of compounds do not display a common technical/structural feature (the substitution pattern although equally defined, differs in all the compounds exemplified namely R1 is never H for compounds of formula (I)) and does not, therefore, qualify as a unifying element.

4. There is a lack of unity a posteriori and the different inventions and/or groups of inventions, not belonging to a common inventive concept, have to be formulated as different subject(s) in the order chosen by the applicant.

5. It is noted that due to the objections under Rule 13(2) PCT in the international invitation dated 08.09.2003, one additional search fee was paid by the Applicant, but unfortunately (after a first refund and consequently extension of the 405 time limit) the applicant neither restricted nor paid additional fees in response to the invitation according to form 405.

The written opinion refers only to the first invention as defined in the invitation dated 08.04.2004.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (invention 1.1):

The present application refers to derivatives of camptothecin with structural modifications of the lactone ring, characterized by a better stability of the molecule in plasma or its hydro solubility for formulatory purposes and also a better therapeutic index.

Although the compounds of chemical formula I and those of many citations overlap, the structural difference to the many novelty destroying prior art documents (for the single example, paragraph, page or table applicant's attention is drawn to the specific passages as quoted in the search report for each of D1 to D6) and invention 1.1 (which the present written opinion refers to) resides mainly in the further modification of homocamptothecins at the 7 position (R1 cannot mean H).

Inventive step (invention 1.1):

The technical problem due to the overlap is thus considered to be the provision of further camptothecin analogs wherein the lactone portion is modified and the 7 position is optionally substituted by and oxime derivative.

However, from the prior art D6:HERTZBERG R P ET AL: "Modification of the hydroxy lactone ring of camptothecin: Inhibition of mammalian topoisomerase I and biological activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 32, no. 3, 1989, pages 715-720, XP002014409, **modifications** of the Hydroxy lactone ring of camptothecin are already known and activity is shown by the data according to table I, page 717.

Since presently only data are provided in terms of IC_{50} values (anticancer activity), but no data are given in favour of an unexpected use of the compounds or surprising effect

of the claimed compound, an inventive step cannot at present be recognized and the examiner cannot evaluate:
a) in view of the more demanding problem as defined by the applicant,
b) wherein the solution of this problem underlying the invention can be seen, and
c) how it can be considered inventive in view of the relevant prior art known so far.

Novelty and inventive step (invention 1.2):
The compound claimed according to claim 10 represents the key intermediate product for the synthesis pathway for the claimed end products. The specific compound differs from all those exemplified in the prior art known so far, in the substituent in position 7 namely the dialkoxymethyl group.
Novelty can b thus recognized.

The relevant Claim 10, relating to an intermediate product, should also fulfil the requirements for patentability which are here synthetised :

a) the claimed intermediate must take part in a process for the preparation of in principle patentable subsequent products,
b) the mentioned intermediate must give a "structural contribution" to the subsequent product,
c) and there should not be any relevant subsequent-product-related prior art as well as intermediate-related-prior art, whose teaching could obviously be used to obtain the desired subsequent product in an analogous process.

The Examiner wishes to express her favourable position with regard to inventive step, points a) and c), of claim 10 (at least "in principle").
It appears that the structural modification of the intermediate compared to those described in D5 (also referred to by the applicant in the description) could be seen as the unobvious solution to the problem of providing a suitable intermediate which allows the functionalisation of position 7 before the modification of the original lactone ring of camptothecin. The skilled person would have not taken any incentive from the mentioned prior art to arrive at the claimed intermediate of laim 10.
Unfortunately the condition according to point b) as above is not satisfied so that a positive opinion cannot be made.